FDA Regulation of Medical Products

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- Among the products that FDA regulates are three categories of diagnostic, preventative, or therapeutic products:
  - Drugs
  - Biologics
  - Medical devices

FDA's functions

- The FDA functions most relevant to countermeasures
  - Review and approval
  - Enforcement
  - Communication
- How these functions are implemented varies somewhat with different types of regulated products.

Review and approval

- In each case the sponsor submits data to seek permission to market its product with specific labeling for a specific purpose.
- No medical product is safe and effective in the abstract; it is only safe and effective for specific uses.
- Those uses are described specifically in the approved labeling.

Risk-benefit analysis

- All medical products present risks. In some cases those risks involve significant toxicity. In all cases, there is a risk that an ineffective product will be used in place of one that would be effective, thus causing the patient harm.
- Risk-benefit analysis can change depending on the conditions in which the product will be used. E.g., a drug used under the supervision of a physician may present less risk than one used without that supervision.

Labeling

- Ultimately, the decisions made in the FDA review are captured in the approved labeling.
  - A product used inconsistent with its labeling may not have data to show that it is either safe or effective for that use.
  - The risk-benefit analysis may change if the conditions of use change.
- All communications by marketers to physicians and patients concerning the product must be consistent with the approved labeling.

Expiration Dating

- Pharmaceutical labeling generally includes an expiration date.
- The expiration date is determined on the basis of FDA review of stability studies performed by the sponsor. Those studies show that, for example, a drug does not degrade to the point that it no longer meets its specifications over a period of two years.
- In some cases, testing may show that the drug would still be within its specifications for a longer period. We will talk later in the program about the government stability testing that leads to permission to use drugs beyond their labeled expiration date is part of the Shelf-Life Extension Program (SLEP).

Enforcement

- Not all medical products go through premarket review at FDA. Over-the-counter drugs and certain types of low-risk medical devices may be marketed without premarket review.
- All medical products must, however, have labeling that is not false or misleading (i.e., the product must not be "misbranded") and all products must not be "adulterated."
- All products that do go through premarket review must be marketed consistent with the conditions under which FDA has permitted such marketing.

FDA enforcement discretion

- FDA enforces the Federal Food, Drug, and Cosmetic Act, and certain related statutes such as provisions of the Public Health Service Act relating to approval of biologic products.
- FDA also enforces its regulations, which are based on those statutes.
- In some cases, as with all law enforcement agencies, FDA recognizes that there are technical violations of its statutes and regulations for which enforcement is inappropriate.

Intended Use

- The concept of “intended use” is central to FDA enforcement efforts with respect to most of the products it regulates. For example,
  - An apricot pit is a drug if it is intended for the treatment of cancer.
  - A drug is misbranded and illegally marketed if it is labeled for one use and intended for another use.

GMPs

- Current good manufacturing practices (GMPs) are the methods by which manufacturers, holders, and transporters of drugs, biologics, or devices assure that every product that they make, hold, or transport is, and continues to be until it is used, safe and effective.
- Failure to comply with GMPs (and for devices, failure to comply with the quality system regulations) makes a product “adulterated” and its distribution or sale illegal.

Safety and Effectiveness Investigations

- To be used in human testing in the United States, in most cases,
  - A drug, including a biologic drug, must be covered by an investigational new drug application (IND);
  - A device must be covered by an investigational device exemption (IDE).
- INDs and IDEs are reviewed by FDA and FDA has the authority to halt investigations proposed to be carried on under these applications.
- IND and IDE regulations require patient safeguards, including in most cases Institutional Review Board (IRB) supervision of investigations, informed consent by subjects, and reporting to FDA.

Premarket review – drugs and biologics

- For drugs, approval is obtained through the submission of a new drug application (NDA) or, for generic drugs, an abbreviated new drug application (ANDA).
- For biologics, approval is through a biologic license application (BLA).

Premarket review – medical devices

- Certain devices, including those that are new or that present significant risks, must undergo premarket review and approval through a premarket approval application (PMA).
- For many other devices, the manufacturer must only submit a 510(k) through which it demonstrates that its product is "substantially equivalent" to a product that is already on the market. FDA "clears" rather than "approves" such devices.
- Some devices are marketed without premarket review but must comply with performance standards.
- Other (generally less risky) devices do not require approval, clearance, or compliance with performance standards, but must not be misbranded or adulterated.

Practice of Medicine

- FDA generally does not regulate the practice of medicine, in the sense that, once a product is approved or cleared, a physician has the freedom to use that product for any purpose, even inconsistent with its labeling. (There are some limited exceptions.)
- But FDA and the courts are very strict in preventing marketers from promoting products for uses for which they are not approved or cleared.

How does this all apply to medical countermeasures?

- Some countermeasures are intended to be used consistent with their approved labeling. For them there is no need for further review/authorization.
- Other countermeasures are intended to be used in ways beyond their approved labeling, e.g.:
  - without a prescription
  - in different dosing regimens
- Other countermeasures are not yet approved for any use.

FDA premarket review of medical countermeasures: EUAs

- In an emergency, the risk-benefit analysis may change.
- If FDA grants a request for an emergency use authorization (EUA), it is finding that, in a particular type of emergency, if the conditions set out in the EUA are observed:
  - An approved product may be used in a way inconsistent with the limitations of the approval, or
  - A product that has not yet been approved may be permitted to be used despite lacking the quantum of data that would be necessary for a full approval.
- Because EUA use is not investigational, no IRB review is required, and reports to FDA of the type required for investigational products are not involved.

Emergency use of investigational products

- In some circumstances, the IND or IDE authority may be an appropriate mechanism for use of an unapproved product during an emergency.
- For example, FDA regulations permit the use of investigational drugs for serious or life-threatening diseases or conditions in certain circumstances:
  - Emergency use IND for individual patients
  - Expanded access trial under an IND (for intermediate-sized patient populations)
  - Treatment IND or treatment protocol under an IND.